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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/728,653	12/01/2000	Wei Han	PH-7118	5964

24348 7590 11/19/2002

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EXAMINER	
LUKTON, DAVID	
ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 11/19/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/728,653	Applicant(s) Han
	Examiner David Lukton	Art Unit 1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sep 10, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-7 and 12-18* is/are pending in the application.

4a) Of the above, claim(s) *17 and 18* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-7 and 12-16* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *2, 3*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Pursuant to the directives of paper No. 7 (filed 9/3/02), claims 8-11 and 19-20 have been cancelled. Claims 1-7, 12-18 remain pending.

Applicants' election of Group 2 (claims 1-6, 8, 12-16, 19 limited to G1 and G4) is acknowledged, as is the elected specie (the compound of example B5, present on each of pages 146 and 163).

Claims 1-7, 12-16 are examined in part; claims 17-18 are withdrawn from consideration.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

On page 174, line 20+ it is asserted that unspecified "compounds of the present invention" exhibit Ki values below 60 *micro*molar in an assay of NS3 protease inhibition. Each of claims 12-16, however, is drawn to a "pharmaceutical" composition. This term implies an assertion of therapeutic efficacy, which is not in evidence.

It is stipulated that the following two claims are enabled:

A method of inhibiting hepatitis C nonstructural protein-3 protease (HCV NS3 protease) comprising contacting HCV NS3 protease with a compound of claim 1 for a time and under conditions effective to inhibit HCV NS3 protease.

A method of inhibiting hepatitis C nonstructural protein-3 protease (HCV NS3 protease) comprising administering a compound of claim 1 to a mammal in need thereof for a time and under conditions effective to inhibit HCV NS3 protease.

Such *in vivo* inhibition does not, in and of itself, translate into an effective therapy of a hepatitis infection. A key issue is whether the NS3 protease can be inhibited to a sufficient degree to cause an actual reduction in population of the virions. Issues such as proper anatomical localization, bioavailability, susceptibility of the claimed compounds to proteases and monooxygenases would have to be addressed. For example, if the virus is replicating at a rate of 100 "units" per day in the absence of the compound, and 90 units per day in the presence of the compound, one could say that inhibition had been achieved. However, if the virus is replicating at a rate of 90 per day in spite of the presence of the compound (of claim 1), the patient's condition will still worsen, and "treatment" will not have been achieved. As it happens, structure/activity relationships are unpredictable. As observed by Tung (WO 98/17679), compounds within that disclosed genus (table 9, pp. 106-107) exhibited more than a 100-fold range of efficacies in the inhibition of HCV NS3 protease. Many of those compounds characterized as exhibiting an inhibition above 100

*micro*molar may have been completely inactive. (See also table I of WO 99/07734). Thus, one question is, can applicants look at a structure and determine its activity, even *in vitro*? And if not, how can applicants make predictions about what will happen *in vivo*? As stated in Ingallinella (*Biochemistry* **37**, 8906, 1998) at page 8906, col 1:

"Neither an effective therapy for hepatitis C-associated chronic hepatitis nor a vaccine for preventing HCV infection has... been developed.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

As it happens, effective treatment of viral infections such as hepatitis cannot be predicted from *in vitro* data alone; undue experimentation would be required to practice the claimed invention. It is suggested that the terms "pharmaceutical" and "therapeutically effective" be deleted at each occurrence

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Claims 1-7, 12-16 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- In claim 1, variable Za is defined (page 182, line 21); the following is recited:

  "Za is H, F, Cl, Br, I.... CF_3, OCF_3, - "

  Note that at the end of this line of text, there is a hyphen which is unattached to anything. This hyphen should be moved to the beginning of the next line. The same issue is also present in the second line of text of the definition of Za. The same issue is also present in the first two lines of text of the definition of Zb, and the first two lines of text of the definition of Zc. See also claims 3-5.

- In claim 3, variable R^{10c} is defined, but does not appear in formula II. Since in claim 3, formula II supercedes formula I, defining R^{10c} appears to be superfluous; moreover, R^{10c} cannot be an alkyl group in formula II. The same issue applies in claim 4.

- Claim 5 not properly subgeneric to claim 4, or to any of claims 1-3. Claim 5 requires that the following group be present at the C-terminus of the peptide:

  -CO-CONH-CH_2-X-NH-Y-Z

  If applicants believe the claim dependence to be correct, applicants are requested to indicate what variable R^{10} (in claim 3) would have to correspond to such that claim 5 is properly subgeneric to claim 4 (or to claim 3).

- In claim 5, variable R^{11} is defined. Applicants are requested to explain where in formula III variable R^{11} may be found.

- In claim 7, on page 224, the first compound recited is the elected specie. In order for this compound to be encompassed by claim 1, variable R^{10} would have to be hydrogen. However, claim 1 precludes this possibility. Accordingly, claim 7 is not properly subgeneric to claim 1.

- Claims 12-16 are indefinite as to the objectives of the "therapeutic efficacy".

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DAVID LUKTON
PATENT EXAMINER
GROUP 1800